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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/870,414	05/30/2001	Anton-Lewis Usala	35626/234825	7087

826 7590 06/10/2004

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EXAMINER	
GUPTA, ANISH	
ART UNIT	**PAPER NUMBER**
1654	

DATE MAILED: 06/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/870,414	USALA, ANTON-LEWIS	
	Examiner	Art Unit	
	Anish Gupta	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 1-6, 16-17, 28, 31, are rejected under 35 U.S.C. 102(b) as being anticipated by Schacht et al. (WO98/55161).

The claims are drawn to a method of treating an ulcer by the administration of a hydrogel matrix comprising gelatin and a long chain carbohydrate.

The reference teaches a biopolymer matrix comprising crosslinked gelatin with polysaccharides such as dextran or xanthan (see abstract). The reference states that "[I]njuries which are eligible for the treatment include but are not limited to chronic ulcera, decubitus wounds and pressure sores, foot ulcers. . ." (see page 15, lines 29-31). This meets the limitation of claim 31The reference states that the biopolymer matrix can be formed into film like dressing to be applied on shallow ulcers (see page 16, lines 7-8). Thus, the reference clearly envisions the treatment of ulcers using the gelatin/polyxaccharide matrix.

The reference states that the hydrogels are prepared by crosslinking of solublized gelatin or gelatin derivatives wherein the "[g]elatin is a denatured form of the connective tissue protein collage." (see page 9, lines 14-22). Note that this statement meets the limitation of claim 3 of the instant application. The polysaccharide such as dextran is then co-polymerized with the gelatin (see page 10, lines 1-5). The reference states that the molecular weight of the dextran is preferably between 10,000 and 100,000 (see page 10, lines 10-11). This teaching of the molecular weight is

within the range claimed in claim 6 of the instant application. The reference also teaches that the matrix can contain molecules which have a known affinity for certain growth factors or would healing promoting substances (see page 13, lines 29-31). These molecules include heparin or functional analogs of heparin such as heparin sulfate (see page 14, lines 1-2 and page 17, lines 24-27). The presence of heparin meets the limitation of claims 16-17 of the instant application. Finally, in the examples the reference teaches that 10 g of gelatin was dissolved in 100 ml of PBS-buffer. It is known in the art that gelatin has a molecular weight of between 15000 daltons (g/mol) and 250,000 daltons (see Hoover 3818111, col. 3, lines 35-40; Note that Hoover teaches Type A and Type B gelatin similar to Schacht on page 9, lines 23-25). Using stoichiometric conversions, the concentration of gelatin used in the reference is between .4mM-6mM. Thus, the concentration of the gelatin used is within the range claimed in claim 2.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

2. Claims 1-10, 14, 16-28, 31-35, and 37-44, 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Usala (US 5824331) in view of Jude et al. and Miller.

The claims are drawn to a method of treating an ulcer by the administration of a hydrogel matrix comprising gelatin and a long chain carbohydrate.

Usala et al. discloses a hydrogel matrix that is allows for long term storage of cellular moieties including islets (see col. 3, lines 8-10). The reference further states that "the matrix **supplementally** over the transplanted device has promoted vascularization in the immediate vicinity of the membrane" (see col. 3, lines 35-39). Further, the matrix provide protection "from nitric oxide and metabolites, which are known to cause cellular death from nuclear damage (apoptosis). The cellular matrix utilizes amino acids and related compounds which serve to inhibit L-arginine from forming nitric oxide through nitric oxide synthase" (see col. 3, lines 55-60). The matrix disclosed primarily contains denatured collagen and a cyroprotectant in the form of dextran (see claims 1, 3, 10, 14 and col. 11, lines 40-65). Further, the reference also states that the matrix

contains a nitric oxide inhibitor such as L-arginine, cysteine, amino guanidine in the concentration range of .01 micro molar to 300 mM (see claim 10). Note that the presence of L-arginine at this concentration range meet the limitation of claims 7-10, 14, 16, 22, 32-35 which require the presence of polar amino acids. Further, the presence of aminoguanidine or cysteine would meet the limitation of those claims requiring the presence of a nitric oxide inhibitor, such as claims 16-24 and the like. The reference also states that adding supplemental amino acids such as glutamic acid increase hydrogen bond formation to surrounding gelatin strands result, thus attracting and immobilizing water and polar groups on other gelatin strands at temperature below 30°C. This immobilization of water reduces cell membrane damage from temperature changes. (see col. 14, lines 60-66). "By increasing the number of hydrogen bonds and increasing disulfide formation, the matrix is more resistant to force at temperature below 30°C" (see col. 15, lines 5-9). Thus, the reference provides motivation to add glutamic acid as a polar amino acid for the increase of hydrogen bond formation thereby meeting the limitation of claims that require the presence of glutamic acid. Finally, the reference states that divalent cation chelators, such as EDTA, are present in the matrix to remove divalent cations that interfere with hydrogen bond formation thereby improving resistance forces, i.e. rigidity of the matrix (see col. 15, lines 15-20). The reference states that the divalent cation chelator is present in a concentration of .001 to 100mM (see claim 10). This concentration range is well within the range claimed in claims 25-27 of the instant application. Note that the with the presence of glutamic acid and EDTA, the composition of the matrix envisages a composition comprising collagen, dextran, glutamic acid (increase hydrogen bond formation), EDTA (remove divalent cations) and cysteine (as the nitric oxide inhibitor). This composition meets the limitation of claim 32-34 of the instant application. Therefore, the Usala discloses the composition for the matrix claimed by the instant application. The difference between the prior art

and the instant application is that the reference does not teach the use of the matrix to treat diabetic foot ulcers.

The reference of Miller teaches that therapy of diabetic foot ulcers includes a method directed towards vascular repair in the ischemic ulcer (see abstract). Further, Jude et al. implicates the deleterious effects of nitric oxide and nitric oxide synthase on diabetic foot ulcers (see page 748 and abstract). Diabetic foot ulcer patients with recurrent ulcers have increased nitrite concentrations (see page 753). The reference states that "persistence of high *i*NOS [nitric oxide synthase] activity could, however, be deleterious to the normal healing process" of diabetic foot ulcers (see page 756). The reference proposes that "[s]elective suppression of *i*NOS activity might therefore be beneficial" (seee page 756). Therefore it would have been obvious to one of ordinary skill in the art to use the composition disclosed in Usala to treat diabetic foot ulcers because the treatment of diabetic foot ulcers can be achieved by the suppression of NOS activity and vascular repair. The composition of Usala achieves both since it promotes visualization and the cellular matrix to inhibit L-arginine from forming nitric oxide through nitric oxide synthase.

3. Claims 1-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Usala (WO00/02999) in view of Miller et al.

The claims are drawn to a method of treating an ulcer by the administration of a hydrogel matrix comprising gelatin and a long chain carbohydrate.

The claims are drawn to a method of treating an ulcer by the administration of a hydrogel matrix comprising gelatin and a long chain carbohydrate.

The reference teaches a composition that is useful in the stimulation of vascularization at a site in a mammal for wound healing. The composition disclosed contains L-glutamic acid at a

concentration of between 2-60mN, L-lysine at a concentration of .5 to 30mM, Arginine at a concentration of 1 to 40mM, Gelatin at a concentration of .01 to 40 mM, L-cysteine at a concentration of 5 to 500 μM, aminoguanidine at a concentration of 5 to μ500, intact collage at a concentration of 0 to 5 mM, EDTA at a concentration of 0 to 10mM, and dextran at a concentration of 0 to 2mM (see page 22, table 3). The gelatin in the composition is denatured collagen (see page 19, line 11). Note that this composition encompasses all of the limitations of all of the claims for the composition and concentration of the agent used, including the most inclusive claim 48 of the instant application. The reference states that the matrix is the ability to stimulate or enhance vascularization in surrounding tissue (see page 16, lines 13-14). The reference states that "the matrix may be used to treat conditions benefited by increased vascularization" (see page 16, lines 24-25). The reference further states that the mode of administration includes injection of the matrix directly onto the site (see page 18, lines 22-24), thereby meeting the limitation of claims 45 and 49. The reference also exemplifies preparations wherein 15mL of the matrix is used in the preparation and examples wherein the subject was injected with 8cc of the matrix (see page 23, lines 25-27 and page 26, example 6), thereby meeting the limitations of claims 30 and 50. The difference between the prior art and the instant application is that the reference does not disclose treatment of diabetic foot ulcers.

However, Miller teach that therapy for the treatment of diabetic foot ulcers includes vascular repair of the ulcers (see abstract). Thus, since the US patent teaches method of treating disorders requiring vascularization, it would have been obvious to use the claimed composition for the treatment of foot ulcers because therapy for diabetic foot ulcers include vascular repair of the tissue.

4. Claims 1-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Usala (US 6231881) in view of Miller et al.

The claims are drawn to a method of treating an ulcer by the administration of a hydrogel matrix comprising gelatin and a long chain carbohydrate.

The reference teaches a composition that is useful in the stimulation of vascularization at a site in a mammal for wound healing. The composition disclosed contains L-glutamic acid at a concentration of between 2-60mN, L-lysine at a concentration of .5 to 30mM, Arginine at a concentration of 1 to 40mM, Gelatin at a concentration of .01 to 40 mM, L-cysteine at a concentration of 5 to 500 µM, aminoguanidine at a concentration of 5 to µ500, intact collage at a concentration of 0 to 5 mM, EDTA at a concentration of 0 to 10mM, and dextran at a concentration of 0 to 2mM (see col. 12, table 3). The gelatin in the composition is denatured collagen (see col. 12, lines 39-40). Note that this composition encompasses all of the limitations of all of the claims for the composition and concentration of the agent used, including the most inclusive claim 48 of the instant application. The reference states that the matrix is the ability to stimulate or enhance vascularization in surrounding tissue (see col. 8, lines 60-67). The reference states that "the matrix may be used to treat conditions benefited by increased vascularization" (see col. 9, lines 10-11). The reference further states that the mode of administration includes injection of the matrix directly onto the site (see col. 8, lines 25-30), thereby meeting the limitation of claims 45 and 49. The reference also exemplifies preparations wherein 15mL of the matrix is used in the preparation and examples wherein the subject was injected with 8cc of the matrix (see col. 13, lines 4-6 and col. 14, example 6), thereby meeting the limitations of claims 30 and 50. The difference between the prior art and the instant application is that the reference does not disclose treatment of diabetic foot ulcers.

However, Miller teach that therapy for the treatment of diabetic foot ulcers includes vascular repair of the ulcers (see abstract). Thus, since the US patent teaches method of treating disorders requiring vascularization, it would have been obvious to use the claimed composition for the treatment of foot ulcers because therapy for diabetic foot ulcers include vascular repair of the tissue.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1-29-31-42, 46-48, and 50-51 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-57 of U.S. Patent No. 6,261,587 in view of

The claims are drawn to a method of treating an ulcer by the administration of a hydrogel matrix comprising gelatin and a long chain carbohydrate.

The US patent claims a method of stimulating visualization at a site in a mammal by contacting the site with a matrix comprising denatured gelatin, dextran, nitric oxide inhibitor and a polar amino acid selected from Arginine, lysine, or glutamic acid (see claim 38). The gelatin is in the form of denatured collagen and is in the concentration range of between .01 to about 40mM of denatured collagen (see claim 44). Note that this concentration range is the same ranged claimed in

claim 2 of the instant application. Further, the concentration of dextran is between 0 to about 2mM (claim 45) and polar amino acid between 3 to about 150 mM (claim 42). Both of the claimed concentration range is with the range claimed in claims 5, 8-9, and 33-36 of the instant application for dextran and the polar amino acids. Moreover, there is also the same concentration ranged claimed for the specific amino acids of glutamic, lysine and Arginine (see claim 43 of the US patent and claim 11-15 of the instant application. The nitric oxide inhibitors claimed in the US patent include dextran, heparin, cysteine, L-arginine, and aminoguanidine (see claims 21, 39-41 of the US patent). These nitric oxide inhibitors, including the concentration claimed in the US Patent, are similar to those claimed in claims 17-24 and 37-44 of the instant application. Note that claim 47 of the US patent claims a composition comprising dextran, denatured collagen, aminoguanidine, glutamic acid, lysine and arginine. This composition is similar to the composition claimed in claim 48 of the instant application. The difference between the US Patent and the claimed invention is that the US Patent does not teach the treatment of diabetic foot ulcers.

However, Miller teach that therapy for the treatment of diabetic foot ulcers includes vascular repair of the ulcers (see abstract). Thus, since the US patent claims are drawn to a method of vascularization, it would have been obvious to use the claimed composition for the treatment of foot ulcers because therapy for diabetic foot ulcers include vascular repair of the tissue.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anish Gupta whose telephone number is (703) 308-4001. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback , can normally be reached on (703)306-3220. The fax phone number of this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Anish Gupta
Patent Examiner